COMMENTS TO DOCKET NUMBER 99N-0193

Federal Register Monday, June 28, 1999 Volume 64, number 123, page 34608. Proposed rule, "Supplements and Other Changes to an Approved Application"

Page 34609. FDA states that there is a difference between "validating the effects of the change" and "validation" required under the current good manufacturing practice regulation. Although the definition under proposed 21 CFR 600.3(ii) is ostensibly different than the definition of "validation" as commonly used in FDA's "General Principals of Process Validation," it appears to me to be a distinction without a difference. Could FDA provide background on how and why it reached its conclusion that cGMP "validation" and "validating the effects of the change" have different meanings? Could FDA explain how this would change the information that is submitted in a supplement to FDA, and in particular, what data that has previously been submitted in supplements would now not be required in these supplements and give some specific examples?

On page 34609, III. 2. FDA states, "...or license application for a biological product but should be retained at the facility and be available for review by FDA at its discretion." Could FDA provide some examples of how a supplement would address "validation of the effects of the change" without addressing process or equipment validation? For example, if a manufacturer of a blood fractionation product was to change the tank in which pasteurization (heating to inactivate possible blood borne viral contaminants) occurs, a supplement would be submitted to CBER. Typically the review would not only look at the final and in-process tests conducted on the product intermediate and final product, but also on what is termed "process or equipment validation." Process (or equipment) validation would be reviewed to assure that the new tank met specifications with regard to materials of construction of the tank (see 21 CFR 211.63; 211.211.65(a) & (b)) , that utilities supplying gases and water to the tank met proper specifications (as well as meeting component specifications to the extent that such materials become part of the product), that equipment and controllers to heat and stir the contents (i.e., the blood product) consistently met their operating parameters, and that all recording devices displayed accurate output signals. Additionally, procedures would be reviewed to assure that they have been updated or revised as appropriate. Any of these points could affect the safety of the product, e.g., lack of proper mixing of the contents may affect the time potential blood borne viral contaminants are exposed to appropriate pasteurization. Can FDA explain what portion of the above scenario fits into the "validation of the effects of the change" and should be submitted when there is a change to CBER, and what portion is "process validation" and should not be submitted in a supplement to the agency, but is appropriate "for review by FDA at its discretion?" Could this information be reviewed in a supplement? I would note that the efficiency and accountability of the agency could be improved if there was a clearer delineation of review and inspectional responsibilities.

Page 34610. In previous Federal Register notices, (July 24, 1997) FDA has asserted (FR Vol. 62. No. 142, "...to reduce unnecessary reporting burdens...") that revision of the change reporting regulations will reduce the burden of reporting changes to the agency. Is this synonymous with reducing the number of reports of changes to the agency? If it is not, could FDA explain what it means by "reducing the burden" e.g., amount of time between submission and approval, amount